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EXAMINER SCHWADRON, R

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Below is a communication from the EXAMINER in charge of this application
COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☐ THE PERIOD FOR RESPONSE:

- a) ☐ is extended to run _____ or continues to run _____ from the date of the final rejection
- b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.
- Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☒ Applicant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 12/24/99 and 2/1/00 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☒ The proposed amendments to the claim and for specification will not be entered and the final rejection stands because:
- a. ☒ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.
- b. ☒ They raise new issues that would require further consideration and/or search. (See Note).
- c. ☐ They raise the issue of new matter. (See Note).
- d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.
- e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: see enclosed note

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.
3. ☒ Upon the filing an appeal, the proposed amendment ☐ will be entered ☒ will not be entered and the status of the claims will be as follows:

Claims allowed: none

Claims objected to: N/A

Claims rejected: 11-15

However:

- ☒ Applicant's response has overcome the following rejection(s): see enclosed note
4. ☒ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because see enclosed note
5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficient reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☒ Other see enclosed note

RONALD B. SCHWADRON
DIRECTOR

Serial No. 08/921060
Art Unit 1644

1. Proposed claim 11 would require a new search of the prior art and potential new rejections over the prior art because the proposed claim recites a new limitation that was not previously recited in the claims under consideration (eg. the pending claim recites a method that uses a dose from about .4 to about 20mg of antibody, while the proposed claim recites that the dose is about .4mg). Said proposed claim changes the scope of the claimed invention and would require a new search of the prior art and potential new rejections over the prior art.

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it does not identify the citizenship of each inventor. The citizenship of Inventors Hanna and Newman has been omitted. Applicant has indicated that a new oath will be provided upon indication of allowance.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title should indicate that the invention involves treatment of B cell lymphoma with anti-CD20 antibody and at least one chemotherapeutic agent.

4. The rejection of claims 14 and 15 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons elaborated in paragraph 5 of the Office Action mailed 7/20/99 is withdrawn in view of applicant's statement in page 2 of the amendment filed 2/1/2000.

5. The rejection of claims 11-15 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons elaborated in paragraph 6

of the previous Office Action is withdrawn because original claims 8-10 appear to encompass use of ^{non radiolabelled} ~~nonlabelled~~ antibody because the specification appears to use the term "C2B8" as meaning a nonradiolabelled antibody.

6. Regarding applicants comments about priority for the claimed invention, the following comments are made. While there is support in the instant application for the method of claims 11-13 (eg. original claims 8-10), there is no support for the claimed invention in pages 15 and 16, and pages 61-62 of the instant specification or in said pages of the specification of 08/149099. Original claims 8-10 were not present in parent application 08/149099 (now US Patent 5,736,137). Regarding columns 30-32 of US Patent 5,736,137 (eg. pages 61-62 of 08/149099), said passages of the specification disclose the use of C2B8 in combination with a therapeutic agent, but do not disclose the scope of the invention of claims 11-13 (eg. use of the antibody recited in section (I) of claim 11). The claimed invention is not disclosed in said passage, because said passage is restricted to the disclosure of the use of C2B8 in combination with a chemotherapeutic agent. There is also no disclosure in application 08/149099 of the claimed invention using C2B8 and "at least one chemotherapeutic agent". There is no disclosure in the parent application of the claimed method that uses a mixture of the chemotherapeutic agents recited in said claim in combination with C2B8.

This issue was discussed with BPS Schwartz on 7/13/99.

Regarding applicants comments about column 32 of US Patent 5,736,137, said column does not disclose or incorporate by reference use of a mixture of chemotherapeutic agents. The material incorporated by reference in column 32 refers to use of the individual agents recited in lines 5-7, not mixtures of said agents.

7. Claims 11-15 are rejected under 35 U.S.C. § 102(e) as being anticipated by Anderson et al. (US Patent 5,736,137).

Regarding the inventors of US Patent 5,736,137, the inventorship is incorrectly listed on said patent. John Leonard was removed as an inventor of said application (see Paper 39 of 08/149099, also see inventors listed on file jacket of said application). Thus, US Patent 5,736,137 constitutes prior art under 35 U.S.C. § 102(e). Anderson et al. teach the use of C2B8 (a particular species of anti-CD20 therapeutic antibody) in combination

Serial No. 08/921060

Art Unit 1644

with a chemotherapeutic agent wherein the agent is administered, as per the times recited in the claims, wherein the agent is one of the agents recited in claim 15.

Applicant has requested that this rejection be held in abeyance pending the submission of a declaration that would change the inventorship in the instant application such that US Patent 5,736,137 would not constitute prior art.

8. Claim 11 is rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kaminski et al. (US Patent 5,595,721).

Kaminski et al. teach the use of a chimeric anti-CD20 antibody for the treatment of B cell lymphoma (see column 7). Kaminski et al. teach the administration of therapeutic anti-CD20 antibody in combination with cyclophosphamide (see column 33). Kaminski et al. teach that said antibody causes apoptosis of cells which are bound by said antibody (see column 33). While Kaminski et al., do not teach that this antibody has the functional characteristics recited in claim 11, part (I), it appears that said characteristics would be found in an antibody that induces apoptosis when bound to target cells. Therefore the claimed method appears to be same or similar to the method of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the method of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Regarding applicants comments as they apply to this rejection, Kaminski et al. teach the use of a chimeric anti-CD20 antibody for the treatment of B cell lymphoma (see column 7). Regarding applicants comments about the disclosure of Kaminski et al., as applicant is well aware, there is no requirement that a specific example of an invention be present in order for the disclosure to be enabled. Kaminski et al. teach that said antibody causes apoptosis of cells which are bound by said antibody (see column 33). There has been no evidence provided that the antibody disclosed by Kaminski et al. (eg. chimeric B1 antiCD20 antibody) does not have the property of causing apoptosis of cells which are bound by said antibody. Therefore, the disclosure of Kaminski et al. is presumed to be enabled. While Kaminski et al., do not teach that this antibody has the functional characteristics recited in claim 11, part (I), it appears that said characteristics would be

Serial No. 08/921060
Art Unit 1644

found in an antibody that induces apoptosis when bound to target cells. Therefore the claimed method appears to be same or similar to the method of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the method of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Regarding applicants comments about nonobviousness, while Kaminski et al., do not teach that this antibody has the functional characteristics recited in claim 11, part (I), it appears that said characteristics would be found in an antibody that induces apoptosis when bound to target cells. Regarding applicants comments about parent application 08/149099, the claims of said application are drawn to a particular species of antibody (eg. C2B8) not recited in the claim rejected in this rejection.

9. Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Press et al. (Blood) in view of Hellstrom et al. (WO 92/07466) and Robinson et al. (US Patent 5,500,362).

Press et al. teach the use of a murine anti-CD20 antibody (see abstract) for the treatment of B cell lymphoma. Press et al. teach that therapeutic anti-CD20 antibody was administered to patients that had received at least one chemotherapeutic agent(see page 586, column 1). Press et al. teach the use of murine anti-CD20 antibody wherein said antibody depletes virtually all peripheral B cells within 24 hours(see Figure 2) wherein the dosage used is encompassed by the range recited in claim 11 (see Figure 2). Press et al. does not teach that the method uses a chimeric antibody with the functional property recited in the claims. While the murine antibody taught by Press et al. has the functional properties recited in claim 11, Robinson et al. teach that it would be expected that a chimeric anti-CD20 would have greater lytic activity in vivo compared to the murine antibody from which it is derived, because the chimeric antibody would possess increased ADCC and CDC (see column 20). Hellstrom et al. teach that chimeric antibodies have increased immune function because they contain human Fc (see page 13). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Press et al. teaches the use of antiCD20 antibody to treat B cell lymphoma, while Hellstrom et al. teach chimeric

Serial No. 08/921060
Art Unit 1644

monoclonal antibody treatment in combination with chemotherapeutic agents can be used to treat cancer and both Hellstrom et al. and Robinson et al. teach the use of chimeric antiCD20 antibody to treat B cell lymphoma and the advantages of using such antibodies. One of ordinary skill in the art would have been motivated to do the aforementioned because Hellstrom et al. teach the use of chimeric antibodies in combination with chemotherapy (see page 7) and Robinson et al. teach the use of chimeric anti-CD20 antibody for the treatment of B cell lymphoma (see column 20). A routineer would have determined the particular time points for administering the antibody as recited in claims by routine experimentation.

Regarding applicants comments as they apply to this rejection, Press et al. (Blood) teach the use of murine anti-CD20 antibody wherein said antibody depletes virtually all peripheral B cells within 24 hours(see Figure 2) wherein the dosage used is encompassed by the range recited in claim 11 (see Figure 2). Press et al. does not teach that the method uses a chimeric antibody with the dose recited in the claims. While the murine antibody taught by Press et al. has the functional properties recited in claim 11, Robinson et al. teach that it would be expected that a chimeric anti-CD20 would have greater lytic activity in vivo compared to the murine antibody from which it is derived, because the chimeric antibody would possess increased ADCC and CDC (see column 20). Hellstrom et al. teach that chimeric antibodies have increased immune function because they contain human Fc (see page 13). Regarding applicants comments about the Anderson declaration, said declaration is drawn to the C2B8 antibody. Said antibody is not recited in the claims under consideration. The scope of the alleged unexpected results in the Anderson declaration is not commensurate with the scope of the claimed invention. Furthermore, Press et al. (Blood) teach the use of murine anti-CD20 antibody wherein said antibody depletes virtually all peripheral B cells within 24 hours(see Figure 2) wherein the dosage used is encompassed by the range recited in claim 11 (see Figure 2). While the murine antibody taught by Press et al. has the functional properties recited in claim 11, Robinson et al. teach that it would be expected that a chimeric anti-CD20 would have even greater lytic activity in vivo compared to the murine antibody from which it is derived, because of increased ADCC and CDC.

Regarding applicants comments about proposed claim 11, said claim has not been entered.

Serial No. 08/921060
Art Unit 1644

10. Claims 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellstrom et al. (WO 92/07466) in view of Robinson et al. (US Patent 5,500,362), Reff et al. (J. Cell. Biochem.) or Reff et al. (Blood) or Anderson et al.

Hellstrom et al. teach that monoclonal antibody treatment in combination with chemotherapeutic agents can be used to treat cancer (see page 4). Hellstrom et al. teach the use of chimeric antibodies in combination with chemotherapy (see page 7). Hellstrom et al. teach that the antibody used in the aforementioned method binds tumor cells. Robinson et al. teach the use of chimeric anti-CD20 antibody treat B cell lymphoma. Hellstrom et al. do not teach that the use of chimeric antiCD20 antibody C2B8 in said method. Reff et al. (J. Cell. Biochem.) teach the chimeric antiCD20 antibody C2B8 and that said antibody binds B cell lymphomas (see entire document). Reff et al. (Blood) teach the chimeric antiCD20 antibody C2B8 and that said antibody binds B cell lymphomas (see entire document). Anderson et al. teach the chimeric antiCD20 antibody C2B8 and that said antibody binds B cell lymphomas (see entire document). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Hellstrom et al. teach that monoclonal antibody treatment in combination with chemotherapeutic agents can be used to treat cancer wherein the antibody used in the aforementioned method binds tumor cells, Robinson et al. teach the use of chimeric antiCD20 antibodies to treat B cell lymphoma, while Reff et al. (Blood) or Reff et al. (J. Cell. Biochem.) or Anderson et al. teach chimeric antiCD20 antibody C2B8 and that said antibody binds B cell lymphomas. One of ordinary skill in the art would have been motivated to do the aforementioned because Hellstrom et al. teach that the aforementioned method can be practiced with antibody that binds tumor cells. In addition, the Reff et al. or Anderson et al. references teach that C2B8 could be used to treat B cell lymphoma. A routineer would have determined the particular time points for administering the antibody as recited in claims by routine experimentation.

Applicants comments about priority for the claimed inventions are addressed in paragraph 6 of this Office action. Regarding applicants comments about Anderson et al., Anderson et al. refers to the Anderson et al. reference disclosed in the PTO-1449 filed 8/29/97 (eg. the 1991 Abstract). It is noted that the Anderson et al. patent, when cited in rejections in the previous Office Action is referred to as Anderson et al. (US Patent 5,736,137). Anderson et al. was published in 1991. Even if the claimed invention had

priority to parent application 08/149099, the claimed inventions are not disclosed in parent application 07/978891. Therefore, the Katz type Anderson declaration filed in the instant amendment would not overcome said reference as prior art.

Regarding applicants about unexpected results, the C2B8 antibody was known in the art as per the Reff et al. (J. Cell. Biochem.) or Reff et al. (Blood) or Anderson et al. references.

11. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

12. No claim is allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 305-3014.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1800-1600



Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644